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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KATCHEVES, KONSTANTINA T	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 07/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/392,682	GRUENERT ET AL.	
	Examiner	Art Unit	
	Konstantina Katcheves	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-35 and 37-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-35 37-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-35 and 37-44 are pending in the present application. The after final amendment and remarks, filed on 26 May 2005, have been acknowledged. Upon reconsideration of the claims and the prior Office action, mailed 28 March 2005, the finality of that action is withdrawn. The present Office action is a non-final rejection.

The examiner understands that the present application has a long prosecution history and hopes, with the present office action, to clarify the issues presented by the instant claims and further the prosecution of the present application. The examiner will set forth the following: (1) the pending rejections in light of Applicant's most recent amendment; (2) complete and detailed discussion of the relevance of the Exhibits filed on 03 December 2001 insofar as they relate to the rejections below; and (3) complete and detailed discussion of the relevance of the Declaration from Dr. Dieter C. Gruenert.

I. Rejections in light of Applicant's Amendment of 26 May 2005.

A. Claim Rejections - 35 USC § 112, first paragraph.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-35 and 38-44 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for replacing a target fragment in a cell *in vitro*, does not reasonably provide enablement for a method of replacing a target fragment *in vivo* or *ex vivo*, wherein the cells are intended for gene therapy use. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The grounds for rejection set forth below are similar to those set forth in the Office action made 03 October 2001 and repeated herein in the interests of completeness.

In prior Office actions the examiner directed Applicant's attention to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation.

The nature of the invention and the breadth of the claims.

The present claims are very broad. The present claims encompass methods of replacing a target fragment in a cell wherein the cell is *ex vivo* and replacing a target fragment in a cell wherein the cell is *in vivo*. See claims 17-35. The claims also encompass a method for gene therapy wherein a replacement fragment is delivered into a cell and corrects a genetic defect. See claims 38-44. This breadth of the invention is punctuated by Applicant's own description of the invention which states that "this method first and foremost concerns a method for *in vivo* and *in vitro* correction of gene defects."

The examiner notes that Applicant has amended the claims to include the limitation "wherein the DNA is delivered by local direct administration." The examiner understands that this limitation is derived from language proposed as a limitation by the examiner. Although this limitation has general support in the specification, given its broadest reasonable interpretation, absent a specific definition in the specification, this limitation could include the general methods of transfection using viral vectors and microinjection, for example, as well as intracorporeal

injection. See Specification page 23, whole page and page 25, line 16. Therefore, the present claims remain very broad and subject to the present enablement rejection.

The nature of the invention is a method of treatment by replacing a target fragment in a gene associated with a disease with an exogenous replacement fragment, which corrects the genetic defect in the disease-associated gene. The delivery of nucleic acid *in vivo* or *ex vivo* for therapeutic purposes constitutes gene therapy.

The state of the art, skill of those in the art and predictability of the art.

An analysis of the prior art, as of the effective filing date of the present application, shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph and Palù et al, p. 1, abstract. The continued major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, lst and 2nd paragraphs.

While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression

must be made before gene therapy becomes a useful technique. See Verma et al., p. 242, col. 2-3 and Palù et al., pp. 10-11 and Luo et al., p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of gene therapy and homologous recombination is high. The area of the invention is unpredictable. As discussed above, the method of *in vivo* or *ex vivo* gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The amount of guidance provide and the presence of working examples.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. There is no direction provided as to how to overcome the obstacles to gene therapy recognized by leaders in the field, particularly low efficiency of delivery of the nucleic acid. There is no direction on how to ensure that cells from the *ex vivo* method would replace, or otherwise out-compete, the endogenous defective cells. There are no working examples disclosed which encompass *in vivo* or *ex vivo* applications of the claimed methods.

The quantity of experimentation necessary to carry out the claimed invention is high, as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to determine how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency and how to obtain a sufficient level of homologous recombination in the target cells to achieve a level which would provide sufficient expression to

induce at least some therapeutic effect. Moreover, if the targeted genetic defect is a dominant negative, one would have to further determine how to ensure replacement of both copies (assuming a single locus gene) of the defective exon.

Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so. Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed method of *ex vivo* or *in vivo* gene therapy for replacing a target fragment using homologous recombination.

B. Claim Rejections - 35 USC § 103

The text of Section 103(a) of Title 35, U.S. Code not included in this action can be found in the Office action mailed 03 October 2001. Upon review of the file, the examiner improperly withdrew the rejection of the claims in view of Vega under 35 U.S.C. 103(a) in the Office action mailed on 24 June 2004. That rejection is reinstated and repeated herein in the interests of clarity.

Claims 17-20, 26-29, 31 and 37-44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Vega (Human Genetics (1991) 87:245-253).

The invention of the instant claims is drawn to a method of gene replacement wherein the replacement DNA comprises providing at least one exon with 3' and 5' flanking regions which are non-coding sequences. The replacement DNA is at least 1-2000 bases in length. Applicant

should note that the claimed method is interpreted as having open language. Although the vector is described using the language "consisting essentially of" this language is generally interpreted as open. Assuming *arguendo*, that "consisting essentially of" is not alone interpreted as open language. The claim is drawn to a method "comprising" certain elements. The method has open language which would render the language, "consisting essentially of" used to describe the vector used in the method as non-limiting.

Vega teaches a method of gene therapy based on the use of homologous recombination using linear double stranded or single stranded DNA fragments derived from genomic DNA covering the mutation in a particular gene. Although the fragment need only cover the mutation and have flanking sequences homologous to the targeted DNA, it can encompass the whole gene, for instance to correct regulatory defects in unexpressed sequence. As a consequence, the replacement fragment may comprise at least one exon and 5' and 3' flanking intronic sequences. The replacement fragment may be associated with recombination active proteins to improve efficiency of targeting. Delivery means taught include microinjection. *Ex vivo* and *in vivo* approaches are taught. See entire document. Vega does not teach that the replacement fragment is about 1 to about 2000 bases.

At the time of the invention, it would have been obvious to one of ordinary skill in the art to use a fragment of less than 2000 bases. One of ordinary skill in the art would have been motivated to do so because Vega teaches that one of the advantages of gene targeting is that the fragment need not cover the whole gene, but rather only the mutation site and sufficient regions of homologous sequence on either side. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

C. Obviousness Double Patenting

Claims 17, 20-26, and 28-36 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9, 10 and 12 of U.S. Patent No. 6,010,908. This rejection if found in the Office action mailed 03 October 2001. Applicant's acknowledgement of the rejection and intent to file a terminal disclaimer stated in the remarks mailed 28 July 2003 is noted.

II. Complete and detailed discussion of the relevance of the Exhibits filed on 03 December 2001.

In response to the Office action mailed on 01 October 2001 and the enablement rejection made therein, Applicant filed a number of exhibits purporting to show the predictability of the art. Applicant in a telephonic interview on 04 April 2005 with the examiner, Konstantina Katcheves, and her primary examiner, James Ketter, Ph.D., Applicant's representative, Karen Canady, indicated that these Exhibits were not fully considered by the examiners that have presided over the present case. Even assuming Applicant's representative is correct in asserting that the examiners assigned to the present application did not fully address each exhibit, a failure to address each and every exhibit presented by Applicant is not *per se* curative of defects in the patent application and claims rendering the claims unpatentable. In order to be fully responsive to this question posed by Applicant's representative, the examiner is including discussion of each of the Exhibits herein.

At the outset, it should be noted that in the Advisory Action mailed 14 December 2001, the examiner states that five of the exhibits provided by Applicant are post-filing date articles. The other two exhibits are post-filing date as well. Applicant is reminding that enablement must be established as of the time of filing. As post-filing date articles, the exhibits filed do not establish the state of the art at the time of filing. Moreover, as set forth in more detailed discussions of each of the Exhibits in prior Office actions and repeated herein, statements are made in several of these post-filing date articles indicated that the state of the art remains unpredictable even years after the filing date of the present application.

A. Exhibit A (National Human Genome Research Institute titled "Results From First Human Gene Therapy Clinical Trial" dated 19 October 1995 (press release)).

Exhibit A is a press release from the National Human Genome Research Institute titled "Results From First Human Gene Therapy Clinical Trial" dated 19 October 1995. This exhibit has been specifically addressed in the in the Advisory Action mailed 14 December 2001 and in the Office action mailed 26 March 2003. Although Exhibit A was not specifically referred to in these actions, the examiner addressed the usefulness of the clinical trial discussed in Exhibit A in establishing the predictability in the art. Phase I clinical trials, such at those discussed in the press release, are used to evaluate safety, determine a safe dosage range, and identify side elects for a method or drug. Phase I trials typically enroll 20-80 patients. Therefore, two or three patients having some success in over 300 clinical trials is an 0.05% "success" rate and clearly predicts a lack of success for gene therapy methods.

Additionally, the press release itself states that "further refinement" of gene therapy is required and that: "as a preliminary investigation into the safety and effectiveness of gene therapy, several aspects of gene therapy remain to be perfected. One of these is more consistent methods of transporting a gene into a cell. . .."

B. Exhibit B (Ferber, D. Gene Therapy: Safer and Virus-Free? Science 23 November 2001 Vol. 294).

In the Advisory Action mailed 14 December 2001 and the Office action mailed 26 March 2003, the examiners specifically addressed the exhibit of Ferber et al. Applicant cites Ferber (Exhibit B) as further evidence that one of skill in the art has a reasonable expectation of success using Applicant's method for gene therapy. The Examiner disagrees. Ferber, published post-filing date in 2001, characterizes Applicant's method as a technique, which "offers a *potential* means to achieve a longtime dream of gene therapy." See. p.1639 box; emphasis added. Indeed, Ferber starts the article with the statement that most non-viral delivery methods "have not been as efficient as viruses in shuttling genes into cells." See p. 1638. The concluding paragraph of the article also states "complex non-viral carriers are a long way from the clinic, but they may offer a glimpse of future gene therapies." See p. 1642. Therefore, one of skill in the art would recognize only that Applicant's method is considered promising, not that it would be successful.

C. Exhibit C (Goncz et al. Expression of 38508 CFTR in normal mouse lung after site-specific modification of CFTR sequences by SFHR Gene Therapy 2001 Vol. 8 pp 951-965).

The Examiners in each of the Office actions of 14 December 2001, 26 March 2003, 13 July 2004 and 28 March 2005 addressed Exhibit C.

Exhibit C, published well after the effective filing date of the present application, is one the few articles showing *in vivo* work. Assuming *arguendo* that this post-filing date article is an accurate depiction of the state of the art at the time of filing, this article does not demonstrate successful *in vivo* use according to the specification. The specification generally teaches the use of liposomes as one method for *in vivo* work. Example 19 is a prophetic *in vivo* example and refers to Example 17 for the preparation of the replacement DNA fragment and Example 15 for the encapsulation. Example 17 does not discuss the preparation of a DNA fragment at all. Example 15 uses DOPE and gramicidin S to prepare liposomes. In contrast, Exhibit C uses four different carriers, none of which consist of DOPE and gramicidin S. Given that efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy, the delivery vehicle used is critical. None of the three delivery vehicles used in Exhibit C was taught or suggested in the instant specification. Thus, Exhibit C does not show the specification was enabled as filed for *in vivo* methods.

Moreover, Exhibit C shows that those of the art are aware that *in vitro* work cannot be extrapolated to *in vivo* work. Exhibit C, states: "one difficulty in going from *in vitro* to *in vivo* experiments is that the conditions relevant to transfer (the delivery vehicle, the target and the route of delivery) are different." See Goncz, Exhibit C, filed 3 December 2001, pp.961-962 bridging paragraph.

D. Exhibit D (Kunzelmann et al. Gene targeting of CFTR DNA in CF epithelial cells Gene Therapy 1996 pages 859-867).

Although Exhibit D was not specifically addressed by the Examiners, the Examiners chose to focus on articles relating to *in vivo* and *ex vivo* methods which speak directly to the enablement question presented in the Office actions. In fact, the examiners addressed the insufficiency of Exhibit D. In the Office Actions mailed on 13 July 2004 and 28 March 2004, the examiner states: "*in vivo* and *ex vivo* methods are suspect for a number of reasons such as whether *ex vivo* cell transplants would out-compete or replace the endogenous defective cells or whether *in vivo* transfection methods would overcome the difficulties in related to transfer of such as the delivery vehicle, targeting of the appropriate cells and route of delivery." Exhibit D show *in vitro* data and therefore does not go to the core of the enablement questions presented. Additionally, as post-filing date art, Exhibit D is not dispositive on the question of enablement at the time of filing.

E. Exhibit E (Goncz et al. Targeted replacement of normal and mutant CFTR sequences in human airway epithelial cells using DNA fragments. Human Molecular Genetics Vol. 7 no.12 1998 pages 1913-1918).

The examiners assigned to the present application addressed Exhibit E in the Office actions mailed 14 December 2001, 13 July 2004 and 28 March 2005. Exhibit E is another post-filing date article published in 1998 and the second showing *in vivo* methods. Like Exhibit C, above, this article fails to overcome the enablement problems facing the *in vivo* use claimed. The specification generally teaches the use of liposomes as one method for *in vivo* work. Example 19

is a prophetic *in vivo* example and refers to Example 17 for the preparation of the replacement DNA fragment and example 15for the encapsulation. Example 17 does not discuss the preparation of a DNA fragment at all. Example 15 uses DOPE and gramicidin S to prepare liposomes. Exhibit E uses Lipofectin, which consists of DOTMA. Given that efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy, the delivery vehicle used is critical. None of the three delivery vehicles used in Exhibit E, were taught or suggested in the instant specification. Thus, this article, like Exhibit C, above, fails to show the specification was enabled as filed for in vivo methods.

F. Exhibit F (Goncz et al. Sequence specific modification of the human beta-globin gene by small fragment homologous replacement Human Gene Therapy vol. 13 2001 pp629-642).

The examiner specifically addressed the post-filing date article, Exhibit F in the Office actions mailed on 13 July 2004 and 28 March 2005. As discussed in detail above, efficiency and sufficiency of delivery is one of the major obstacles to overcome in gene therapy; thus, the delivery vehicle used is critical. The method of Exhibit F involve the *ex vivo* modification and subsequent transplantation method of isolated cells, which fails to fully enable the claims. The *ex vivo* data fail to overcome the unpredictability of the art because they fail to show that the modification would be maintained *in vivo* because transplantation of the cells into an animal host is not shown. Additionally, the *ex vivo* data do not show that the cells would be replace or out compete endogenous defective cells.

G. Exhibit G (Goncz et al. Sequence specific modification of the human beta-globin gene by small fragment homologous replacement (SFHR), Working Group Meeting Sept. 24, 2001, abstract).

Exhibit G was discussed in the office action mailed 28 March 2005 and 13 July 2004 by the examiner. Again, Exhibit G is post-filing date art that fails to establish the state of the art at the time of filing. In prior remarks, Applicant assert that the ex vivo data of Exhibit G, file 3 December 2001, show that SHFR remained stable in human hematopoietic stem/progenitor cells for 5 weeks in up to 70% of the alleles *ex vivo*. First, for reasons similar to those discussed above, the *ex vivo* data fail to overcome the unpredictability of the art because they fail to show that the modification would be maintained *in vivo* because transplantation of the cells into an animal host is not shown. Additionally, the *ex vivo* data do not show that the cells would be replace or out compete endogenous defective cells.

III. Discussion of the Declaration from Dr. Dieter C. Gruenert filed 29 September 2003.

The Declaration filed by inventor, Dr. Dieter C. Gruenert, filed pursuant to 37 C.F.R. 1.132 has been addressed in the Office actions of 13 July 2004 and 28 March 2005.

The Declaration teaches the SFHR-mediated modification of ion transport in nasal mucosa in a mouse model of cystic fibrosis. Applicant asserts that the instant declaration establishes that the present method works both *in vivo* and *ex vivo*. The declaration points to the disclosure of two exhibits in support of this position. These exhibits are discussed below. The *ex*

vivo results of the Prokopishyn et al. method (Exhibit A) first fail to overcome the short coming of in *vivo* gene therapy methods. Second, regarding *ex vivo* methods, the disclosure teaches that nude mouse models were used. Another factor in the efficacy of gene therapy methods is the immune system of the host organism. Whole animals have a sophisticated immune system that must be overcome for the effective *in vivo* transfection of cells where the mouse models have compromised immune systems. The mouse models used by Prokopishyn et al. are immune compromised NOD/SCID mice wherein engraftment of transfected cells would face fewer obstacles presented by the host immune system. Even with these immuno-compromised hosts, the best data found in Prokopishyn et a1. show 13 of 23 surviving mice with engrafted cell. This data, however, fails to provided direction on how to ensure that *ex vivo* modified cells method would replace, or otherwise out-compete, the endogenous defective cells and provide the desired correction.

Goncz et a1. (Exhibit B), cited in the declaration, only teach the *in vitro* microinjection of isolated human hematopoietic stem/progenitor cells and site-specific conversion of approximately 50% of these cells. The examiner does not dispute that the present method is enabled for *in vitro* practices. However, *in vitro* data does not overcome the weight of the evidence already of record that the present invention is not enabled for the full scope of the invention claimed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Konstantina Katcheves whose telephone number is (571) 272-

0768. The examiner can normally be reached on Monday, Tuesday, Thursday and Friday 7:30 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Konstantina Katcheves
Examiner
Art Unit 1636

JAMES KETTER
PRIMARY EXAMINER